Case Report

Obstetric Medicine

Loeys–Dietz syndrome in pregnancy

Obstetric Medicine
2021, Vol. 14(1) 42–45

DOI: 10.1177/1753495X19852819
journals.sagepub.com/home/obm
SAGE

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Abstract

Loeys–Dietz syndrome is a recently described condition which causes cardiovascular, craniofacial, neurocognitive and skeletal abnormalities due to mutations in components of the transforming growth factor-β signalling pathway. Associated vascular abnormalities include vessel tortuosity and an increased incidence of vascular dissection. Pregnancy increases the risk of aortic dissection compared to non-pregnant individuals and an underlying condition such as Loeys–Dietz syndrome increases this further. While aortic dissection is well described in pregnancy in Loeys–Dietz syndrome, some women can have uncomplicated deliveries, particularly when the risks of the condition are actively managed. Such pregnancies should be considered high-risk, and women should be counselled and managed accordingly. Here we describe two pregnancies in one woman, both with successful outcomes, followed by a summary of the key management principles.

Keywords

Loeys–Dietz syndrome, aortic dissection

Date Received: 26 November 2018; accepted: 3 May 2019

Introduction

Loeys–Dietz syndrome (LDS) was first described in 2005 and results from a variety of mutations in the TGF-β receptor or signalling pathway.[1] Connective tissue abnormalities in this condition cause aggressive vascular disease with a high incidence of aortic dissection and other vascular complications.[2] Pregnancy also causes an increased risk of aortic dissection due to increased haemodynamic stress on the aorta and changes in plasma concentration of oestrogen and progesterone. The combination of pregnancy and Loeys–Dietz syndrome potentially puts these women at very high risk of aortic dissection during pregnancy and the postpartum period, which should therefore be reflected in careful pre-pregnancy counselling, and close attention in the antenatal and postnatal periods.[3]

Case

A 22-year-old woman in her first pregnancy was referred for review because of a known diagnosis of Loeys–Dietz syndrome. Her mother had suffered two separate episodes of aortic dissection, the second of which occurred six months postpartum and was fatal. The woman's brother had also died at the age of eight from an aortic dissection. Genetic evaluation of the woman confirmed she had a mutation in *TGFBR1*. Past medical history was also notable for Langerhans cell histiocytosis, which was incidentally diagnosed following cross-sectional imaging performed when she developed abdominal pain. She had depression and had stopped taking citalopram prior to conception. She had reported two previous miscarriages, both of which required surgical evacuation of retained products of conception.

Prior to this pregnancy, transthoracic echocardiography had shown that her aortic root was 38–40 mm in diameter. She had normal ventricular function and no aortic or mitral valvular pathology. She had been taking losartan 50 mg daily prior to conception.

At booking her body mass index was 18.6 kg/m^2 and blood pressure 94/65 mmHg. She had smoked up to 20 cigarettes per day prior to pregnancy and stopped in early pregnancy. On examination, she was 176 cm tall, had mild scoliosis, a highly arched palate and ligamentous laxity.

During this pregnancy she commenced 1.25 mg bisoprolol at 14 weeks of gestation, which was increased to twice daily at 24 weeks of gestation. She was followed-up regularly in a joint obstetric/cardiac clinic. Regular echocardiography showed no change in aortic root diameter. Flexion/extension views of the cervical spine showed no subluxation. MRI of the spine showed dural ectasia at the level of L5, S1 and S2. Fetal anomaly scan at 20 weeks of gestation showed normal growth and no structural abnormality.

The woman was admitted electively to the ward for observation at 32 weeks of gestation, and an elective caesarean section was planned for 34 weeks of gestation after parenteral steroid administration. The mode and timing of delivery was discussed extensively, given the need to balance fetal risks of preterm delivery against maternal risks of aortic dissection and uterine rupture. She was deemed to be at very high risk of complications of LDS given her strong family history of

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fatal aortic dissection. While on the ward, she went into spontaneous labour and underwent an uncomplicated caesarean section at 33 weeks. A male infant weighing 2.4 kg was delivered in good condition, with Apgars of 9, 9 and 10 at 1, 5 and 10 min, respectively. He was taken to the special care baby unit for respiratory support. Her son underwent genetic testing and the same mutation in *TGFBR1* as in the proband was identified.

Postnatally she breastfed her infant for six months, and when she stopped breastfeeding she restarted losartan 25 mg twice daily. She had no change in echocardiographic findings postnatally. Subsequent MR angiogram showed that she had developed focal aneurysmal dilatation of the infra-renal abdominal aorta, compared to a CT angiogram performed five years prior to pregnancy. The left vertebral artery was patent on the previous imaging, but appeared occluded and hypoplastic in segments on the MR angiogram, consistent with previous thrombosis or dissection. On questioning, the woman reported previously attending hospital prior to pregnancy with a severe headache without any neurological deficit. She was discharged after an unremarkable CT head (without angiogram) and lumbar puncture.

She then unexpectedly became pregnant for a second time 2.5 years later and was changed from losartan to bisoprolol in early pregnancy. Her pregnancy was complicated by the identification of severe hypothyroidism for which she was treated with increasing doses of levothyroxine. She underwent cardiac MRI and regular echocardiography. MRI showed that the dimensions of the abdominal aortic aneurysm remained stable. Her aortic root and ascending aorta were unchanged on serial echocardiography. An anomaly scan detected no abnormalities. She was admitted for an elective caesarean section at 33 weeks and six days of gestation with epidural anaesthesia and received parenteral corticosteroids prior to this. A female infant in good condition was delivered, weighing 1972 g with Apgars of 7, 10 and 10 at 1, 5 and 10 min, respectively. Tubal ligation was also performed. Cord bloods were taken for genetic testing, which showed no mutation. The woman remained on the antenatal ward for a week after delivery and started enalapril for blood pressure control. The woman decided to continue with breastfeeding after discussion regarding the potential contribution of lactation to the risk of dissection in the postpartum period. Following the cessation of breastfeeding, the woman stopped enalapril and started losartan 50 mg once daily.

An MRA of the woman's aorta during her second pregnancy revealed that her ascending aorta was expanding, measuring 33 mm $\times$ 31 mm compared to 30 mm $\times$ 30 mm on previous imaging. Her aortic root was stable at 36 mm. After this pregnancy, echocardiography showed her aortic root had increased in size to 42 mm and elective aortic root replacement (sparing her aortic valve) was performed. An intraoperative transoesophageal echocardiogram revealed a competent aortic valve, an aortic root aneurysm and good biventricular function. Her ascending aorta was found to be normal but her aortic root measured 39 mm and was replaced with a 28 mm Valsalva graft. A postoperative echocardiogram confirmed her aortic valve had remained competent with no change in biventricular function. There were no immediate complications and she was admitted to cardiac intensive care following the procedure. She was transferred to a ward after two days and discharged on day 5.

Discussion

Loeys–Dietz syndrome

Loeys–Dietz syndrome is associated with mutations in the TGF-β receptors and further downstream in the TGF-β. Mutations in five genes have been identified: *TGFBR1*, *TGFBR2*, *TGFBR3*, *SMAD3* and *TGFB2*. The pattern of inheritance is autosomal dominant, and de novo cases are not infrequent. The phenotype seen in individuals with LDS is variable, both within and between different families. The condition can be identified on clinical features alone, but there are no specific clinical diagnostic criteria. Diagnosis is then confirmed with genetic analysis. Patients should receive genetic counselling during this process.[1–3]

Individuals with Loeys–Dietz syndrome have cardiovascular, craniofacial, neurocognitive and skeletal abnormalities and can have considerable overlap with Marfan syndrome and vascular Ehlers–Danlos.[1,2] Individuals typically have hypertelorism, bifid uvula, and velvety, thin translucent skin with easy bruising. They may also have cleft palate and craniosynostosis. Joint hypermobility is seen frequently and should be treated with occupational therapy and physiotherapy.[3]

Individuals with LDS may suffer from aggressive vascular disease, with aneurysms and dissections seen throughout the vascular tree. There is a high incidence of aortic root dilatation, aortic aneurysm and dissection, which can occur even in childhood. Generalised vascular tortuosity is often present, though usually asymptomatic.[1–4]

Loeys–Dietz syndrome in pregnancy

There have been a number of cases of Loeys–Dietz syndrome in pregnancy reported and these are summarised in a recent review.[5] These pregnancies should be considered high risk with regards to aortic dissection. There is also increased risk of other vascular complications and two cases of uterine rupture have been reported. Risks are particularly high during the third trimester and are highest in the postpartum period.

Due to the nature of these pregnancies, discussion prior to conception is vital. This should cover contraception, the inheritance pattern of the condition and genetic testing options, including preimplantation genetic diagnosis, or testing early in pregnancy (for example with chorionic villus sampling or amniocentesis) for women in whom the mutation has been identified, who would consider termination of the pregnancy if the fetus is affected. Alternatives to pregnancy should be discussed, including surrogacy, gamete donation and adoption.

Women require frequent monitoring of their aortic root (usually through echocardiography) and good blood pressure control. Angiotensin II receptor blockers are preferred in non-pregnant individuals as their ability to attenuate TGF-β signalling may reduce the risk of progression of aortic aneurysm.[6] Due to concerns about the use of ACE inhibitors and angiotensin II receptor blockers in pregnancy, these medications should be stopped when pregnancy testing reveals a positive result. Beta-blockers are the preferred first line agent for blood pressure in pregnant women with Loeys–Dietz syndrome.[3]

Management in pregnancy

There are many uncertainties regarding optimum management of women with Loeys–Dietz syndrome and pregnancy, due partly to scarcity but also due to the substantial phenotypic variability within the Loeys–Dietz spectrum. Advice must be extrapolated from other aortic pathologies. The particular management strategy we advocate at our centre is summarised in Table 1.[5,7–12] In particular, we recommend referral to a specialist centre, pre-conception counselling, good blood pressure control and close surveillance of their vascular tree. Women are advised to deliver in centres with access to a special care baby unit, as well as vascular and cardiothoracic services.

Table 1. The management priorities in a pregnant woman with Loeys–Dietz syndrome (based on ESC guidelines.[8])

Pre-conception	
Genetic considerations	If mutation known, offer pre-implantation genetic diagnosis or early pregnancy testing if termination of an affected fetus would be considered
Imaging	Imaging of vascular tree (MRI or CT) ideally prior to pregnancy Echocardiogram
Aortic root replacement	Consider if aortic diameter is greater than 45 mm though risk of dissection may remain elevated below this diameter in LDS
General pregnancy advice	Folic acid (dose depending on local policy) for three months pre-conception
Advise against pregnancy	If aorta is greater than 45 mm (or greater than 40 mm in a woman with family history of dissection or sudden death)
Obstetric	
General obstetric advice	Adequate vitamin D replacement and folic acid replacement according to local guidelines Aspirin as per local guidelines for pre-eclampsia risk reduction
Venous thromboembolism prophylaxis	Risk stratification and risk/benefit decision discussed on individual basis
Mode of delivery	*ESC guidelines (for aortic conditions; not specific to LDS)* Ascending aorta less than 40 mm: vaginal delivery is recommended Ascending aorta 40–45 mm: either vaginal delivery with epidural anaesthesia and expedited second stage, or caesarean section can be considered Ascending aorta greater than 45 mm: caesarean section should be considered If ascending aortic dissection occurs and fetus viable, emergency caesarean section and immediately proceed to repair
Timing of delivery	Preterm delivery is often advocated but no studies to support or refute this approach
Location of delivery	Specialist centre with cardiothoracic surgery support Special care baby unit on same site
Management of postpartum haemorrhage	Ergometrine and carboprost are relatively contra-indicated because of the risk of hypertension
Medical	
Blood pressure control	Meticulous blood pressure control (aim to keep less than 130/80 mmHg) Beta-blockers are agent of choice Discontinue angiotensin II blockers when pregnancy test positive
Assessment of vascular tree	MRI (without gadolinium if possible) if not performed pre-conception or if abnormalities are identified that require monitoring
Aortic root assessment	Regular echocardiography (every 4–12 weeks, but consider monthly if aortic dilatation present)
Prophylactic aortic surgery	If aortic diameter is greater than 45 mm and increasing rapidly
Fetal	
Fetal genotype identification	If the maternal genotype is known, offer invasive testing, e.g. chorionic villus sampling or amniocentesis (if the result would alter a decision to continue the pregnancy). Cord blood can be taken at delivery for genetic testing if antenatal testing is not performed.
Anaesthetic	
Cervical instability	Plain films in flexion and extension
Dural ectasia	MRI spine

CT: computed tomography; ESC: European Society of Cardiology; LDS: Loeys-Dietz syndrome; MRI: magnetic resonance imaging.

Mode of delivery

With no large studies available to help guide the correct approach, debate remains regarding the optimum mode of delivery. Women with Marfan syndrome can deliver vaginally without complication, and caesarean section is generally not considered in these women unless aortic diameter exceeds 40 mm, and not recommended unless aortic diameter exceeds 45 mm.[8] However, the infrequent occurrence of uterine rupture in pregnant women with Loeys–Dietz syndrome and the uncertainty regarding the risk of dissection in women with LDS even with a normal aortic diameter has led to an increased concern about advocating a vaginal delivery in these women, particularly towards term. Recommendations from the recent ESC guidelines for cardiac disease in pregnancy are summarised in Table 1.[8]

Timing of delivery

There were two women in the earliest series of LDS published whose pregnancies were complicated by uterine rupture.[2] The gestation at which these events occurred is not stated. This therefore led clinicians to be anxious about the risk of rupture in the presence of an enlarging gravid uterus, assuming that risk increased with uterine size. However, many more cases of pregnancy in LDS have been reported since that early publication, with no further pregnancies complicated by uterine rupture.[5] It is therefore difficult to advocate that preterm delivery is of benefit in all women with LDS, given the risks of fetal morbidity in this setting. The decision to deliver prior to term should be made on a case-by-case basis.

Management at and after delivery

It is common practice to use synthetic oxytocin at the time of delivery to reduce the risk of postpartum haemorrhage. There are no data available to guide the use of oxytocin and the method by which this is administered (bolus or infusion) but animal models suggest it may be beneficial to avoid use of these agents if possible.[13]

These women display an increased risk of aortic dissection for weeks to months postpartum, even with adequate blood pressure control. This could be due to elevated levels of oxytocin, and experiments with animal models suggest that blockade of oxytocin postpartum reduces the rate of aortic dissection.[13] Women should be warned regarding symptoms of aortic dissection.

As oxytocin levels are maintained during breastfeeding, women must receive advice regarding the theoretical increased risk of aortic dissection. Those women choosing to breastfeed can safely be offered ACE inhibitors such as enalapril or captopril, but should not restart ARBs until cessation of breastfeeding.[5]

Conclusions

Loeys–Dietz syndrome is an uncommon but important condition, which demands careful multi-disciplinary care prior to, during and after pregnancy. The current management strategy of pregnant women with this condition was influenced by initial reports of a high rate of complications. However, it is not clear whether this approach should apply to all women with all the mutations now described or whether genotype- and phenotype-tailored strategies are more appropriate, and the optimum management strategy remains unknown.

Acknowledgements

We would like to thank the patient for permission to publish this case report.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

The patient provided informed written consent for publication.

Guarantor

KET is the guaranteeing author for this paper and guarantees the manuscript's accuracy and the contributorship of all co-authors.

Contributorship

KET, JH and CJF drafted the manuscript. LM, AP and EB edited the manuscript and provided critical revisions of the manuscript. All authors approved the final manuscript.

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